REMARKS

Entry of the foregoing, reexamination and further and favorable reconsideration of the subject application in light of the following remarks, pursuant to and consistent with 37 C.F.R. § 1.112, are respectfully requested.

Applicants thank the Examiner for taking the time to discuss the outstanding Office Action with Applicant's representative on December 18, 2002.

As indicated in the Office Action Summary, claims 1-25 and 27-33 are pending in the instant application. By the present Amendment, claims 1, 6 and 9 have been amended to more precisely define the claimed invention. These amendments derive support from throughout the specification and claims as originally filed, especially on page 5, lines 6 and 22 and page 12, line 35 to page 13, line 20. No new matter has been added by way of the present Amendment. Claims 21, 22 and 25 have been canceled by way of the present Amendment. Applicant reserves the right to file a continuation or divisional application directed to any subject matter deleted or amended by way of the present Amendment.

Objections to the Claims/
Rejections under 35 U.S.C. § 112 First Paragraph

The amendments to the claims filed on January 18, 2000 and March 12, 2001 stand objected to because the amendments purportedly introduce new matter into the disclosure. In addition, claims 1-22, 32 and 33 stand rejected under 35 U.S.C. § 112, first paragraph, as purportedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Specifically, the Examiner rejects the recitation of "all of a sequence of a full-length gene".

By way of the present Amendment, independent claims 2 and 9 have been amended to remove the language "all of a sequence of a full-length gene" and the

term "cDNA" has been added, as suggested by the Examiner. Thus, Applicants submit that these objections and rejections are obviated.

Claim Rejections -35 USC §112, second paragraph

Claims 1-25 and 27-33 are rejected under 35 USC § 112, second paragraph, as purportedly indefinite.

Claim 1 stands rejected for the recitation of "which fragments are selected from the group consisting of one or more nucleic acid fragments and one or more PNA fragments and have all of a sequence of a full-length gene" because it is purportedly unclear how the "fragments" relate to the full length gene.

By way of the present Amendment, independent claims 2 and 9 have been amended to remove the language "all of a sequence of a full-length gene" and the term "cDNA" has been added, as suggested by the Examiner. Applicant submits that as the claims now recite "cDNA" if would be clear to the skilled artisan as to what is claimed. Applicant requests that this rejection be withdrawn.

Claims 1-8 and 19-21 stand rejected for the recitation in claim 1 of "binding a labeled protein", because it is purportedly unclear as to what the labeled protein is binding. By way of the present Amendment, independent claims 2 and 9 have been amended to recite "binding a labeled protein specifically to a mismatched base pair", as suggested by the Examiner. Thus, Applicant requests that this rejection be withdrawn.

Claims 1-8 and 19-21 stand rejected for the recitation in claim 1 of "between the hybridized fragments having a mutation" because the recitation purportedly lacks proper antecedent basis in step (A) and because it is unclear which if any fragments have a mutation. As suggested by the Examiner, claim 1 has been amended to provide antecedent basis by inserting the end of step (A) "thereby hybridizing fragments having a mutation". Thus, Applicant requests that this rejection be withdrawn.

Claims 1-8 and 19-21 stand rejected for the recitation in claim 1 of "detecting the label" because the recitation purportedly lacks proper antecedent basis in step (B) which recites, "labeled protein". As suggested by the Examiner, claim 1 has been amended to recite antecedent basis. Thus, Applicant requests that this rejection be withdrawn.

Claim 6 stands rejected for the recitation "introducing a label into a nucleic acid" because the recitation purportedly lacks proper antecedent basis in Claim 1 which does not recite a step for nucleic acid labeling. Claim 7 stands rejected for the recitation "the label introduced into the nucleic acid", because the recitation purportedly lacks proper antecedent basis in Claim 1 which does not recite a step for nucleic acid labeling. Claim 6 has been amended to recite antecedent basis. Thus, Applicant requests that this rejection be withdrawn.

Claims 9-18 and 22 stand rejected because claim 9 is purportedly missing steps (B) and (C). Applicant respectfully submits that claim 9 is not missing any steps. Instead, the steps of the claim correspond to the steps as described in the specification. Claim 9 recites steps (A), (D), (E) and (F), because these steps are referred to and described in detail in the specification as steps (A), (D), (E) and (F). *See* the specification, pages 12-13. Thus, Applicant submits that is would be clear to the skilled artisan upon reading the specification as to why claim 9 recites only steps (A), (D), (E) and (F). Thus, Applicant requests that this rejection be withdrawn.

Claims 9-18 and 22 stand rejected for the recitation in claim 9 of "which fragments are selected from the group consisting of one or more nucleic acid fragments and one or more PNA fragments and have all of a sequence of a full-length gene" because it is purportedly unclear how the "fragments" relate to the full length gene. By way of the present Amendment, independent claims 2 and 9 have been amended to remove the language "all of a sequence of a full-length gene" and the term "cDNA" has been added, as suggested by the Examiner. Thus, Applicant requests that this rejection be withdrawn.

Claims 9-18 and 22 stand rejected for the recitation in claim 9 of "between the hybridized fragments" because the recitation lacks proper antecedent basis in step (A). As suggested by the Examiner, claim 9 has been amended to provide antecedent basis by reciting "thereby hybridizing fragments having a mutation" at the end of step (A). Thus, Applicant requests that this rejection be withdrawn.

Claim 21 stands rejected for the recitation "said nucleic acid or PNA" because the recitation purportedly lacks proper antecedent basis in Claim 1 which recites "nucleic acid fragments" and "PNA fragments". Claim 22 stands rejected for the recitation "said nucleic acid or PNA" because the recitation purportedly lacks proper antecedent basis in Claim 9, which recites "nucleic acid fragments" and "PNA fragments". Claims 21 and 22 have been canceled herein as redundant in light of the amendments made in this Amendment. Thus, Applicant requests that this rejection be withdrawn.

Claims 28-31 stand rejected for the recitation in claim 28 of "are fixed in a hybridizable condition" because "hybridizable condition" is purportedly a relational phrase which requires definition or criteria for determining. Applicant submits that the skilled artisan would know what is meant by "hybridizable condition". The specification recites "[t]he hybridization of the fragments fixed on the substrate and the fragment to be assayed for mutations can be performed in a conventional manner". *See* specification, page 7, lines 16-18. Further, Applicant submits that the process of hybridizaton is extremely well known in the art, and thus the skilled artisan would know, and have ready access to sources of information regarding, what conditions are favorable for hybridization. Thus, Applicant submits that is would be clear to the skilled artisan upon reading the specification what is meant by "hybridization condition". Applicant requests that this rejection be withdrawn.

Claim Rejections - 35 USC §102

Claims 1- 3, 6-8, 19, 20 and 28-30 stand rejected under 35 U.S.C. § 102(e) as purportedly anticipated by Chee *et al.* (U.S. Patent No. 5,861,242).

Chee *et al.* is cited for purportedly disclosing a method for detecting a nucleic acid fragment having a mutation comprising hybridizing fragments fixed on a substrate wherein the fragments are nucleic acid fragments and have all of a sequence of a full-length gene (HIV reverse transcriptase) with at least one nucleic acid fragment of which a mutation is to be assayed. Applicant respectfully traverses.

In order to anticipate a claim under 35 U.S.C. §102(b), a reference must teach every element of the claim. *See* MPEP 2131 *et seq.* Further, for proving anticipation, "anticipation requires the presence in a single prior art disclosure of all elements of a claimed invention as arranged in the claims." *Jamesbury Corp. v. Litton Industrial Products, Inc.* 225 U.S.P.Q. 253, 256 (Fed. Cir. 1985). The cited reference does not describe, or even suggest, all of the elements of the rejected claims.

The present claim recites a hybridization step, where a reference and a target hybridize, as an essential element of the invention. Applicants submit that the reference sequence of the chip of Cree *et al.* does not hybridize with the target sequence. Instead, Cree *et al.* disclose that the reference sequence and the target sequence are the same sequence. Specifically, the reference sequence and the target sequences are sense sequences and not complementary sequences. Thus, they cannot hybridize with each other. Applicants refer the Examiner to Figure 6 of Cree *et al.*, which illustrates that the wild type sequences (reference sequence) and mutant sequence (target sequence) have the same sense sequence. By definition, sense sequences cannot hybridize.

Further, the chip of Cree *et al.* is designed according to a tiling strategy (*see* column 6, line 18). The method known as "tiling" comprises the overlapping of more than one oligonucleotide sequences in order to cover a longer sequence. In fact, the chip consists of at least 4 sets of oligonucleotide probes of 9 to 21 nucleotide in length (*see* column 1, lines 65-67). Therefore, the target sequence of Cree *et al.* hybridizes to the short oligonucleotide probes and not to the reference sequence.

In contrast the present invention requires hybridization as an essential method step. Further, the present invention, as amended herein, only requires one full-length cDNA in order to detect a gene of interest, rather than the tiling of oligonucleotides disclosed by Cree *et al.* Thus, the present invention is not anticipated by Cree *et al.* Applicants request that this rejection be withdrawn.

Claim 25 stands rejected under 35 U.S.C. § 102(b) as being purportedly anticipated by Fleck *et al.* Fleck *et al.* purportedly disclose a protein specifically bindable to a mismatched base pair wherein the protein is a C°C mismatch binding protein which specifically binds to C°C mismatched base pairs. Applicants respectfully traverse. In the interest of expediting prosecution, claim 25 is canceled herein without prejudice or disclaimer thereto. Thus, Applicants submit that this rejection is moot.

Claim Rejections - 35 USC §102/103

Claims 1-4, 19-21, 28-32 stand rejected under 35 U.S.C. § 102(b) as purportedly anticipated by or, in the alternative, under 35 U.S.C. § 103(a) as purportedly obvious over Wagner *et al.* (WO 93/02216) as defined by Sambrook *et al.*. Wagner *et al.* purportedly disclose a method for detecting nucleic acid fragments having a mutation comprising hybridizing at least one nucleic acid fragment, with at least one nucleic acid fragment of which a mutation is to be assayed, binding a labeled substance, identifying a fragment bound by the labeled substance by detecting the label to thereby detect a nucleic acid having a mutation wherein the at least one fragment is fixed on a substrate and wherein the fragment fixed on the substrate is cDNA (as prepared by method according to the methods of Sambrook). The Office Action notes that Wagner *et al.* is silent with regard to a hybridization partner having all of a sequence of a full-length gene.

Applicants respectfully traverse. The requirements for a rejection under 35 U.S.C. § 102 are set forth above. The requirements of a *prima facie* case of

obviousness are set forth in M.P.E.P. § 2143 and *In re* Vaeck, 20 U.S.P.Q.2d 1438, 1442 (Fed. Cir. 1991):

> To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations.

The Office Action states that Wagner et al. prepare cDNA as disclosed in Sambrook *et al.*, and that Sambrook *et al.* disclose the preparation of "long" cDNAs. Applicants respectfully submit that Sambrook does not disclose or suggest the preparation of a full-length cDNA, as recited by the claims amended herein. Instead, Sambrook *et al.* describe the preparation of cDNAs of various length (*i.e.*, the preparation of ESTs) but do not teach how to prepare full-length cDNAs. Applicants submit that the preparation of a full-length cDNA is very different from the preparation of a "long" cDNA. Further, the preparation of full-length cDNA is not a "standard method". It is quite difficult to obtain full-length cDNAs.

In fact, without a precise and specific reference to full-length cDNAs in the cited references, there is no suggestion or motivation for the skilled artisan to attempt to prepare or even to attempt to use a full-length cDNA. Further, Wagner *et al.* disclose EST sequences. It would have been an undue burden for the skilled artisan to use the ESTs disclosed by Sambrook *et al.* and Wagner *et al.* to arrive at the full-length cDNAs of the claimed invention. The Office Action does not provide a motivation for the skilled artisan to attempt to overcome this hurdle.

Further, the Office Action states, on page 10, last paragraph, that Sambrook *et al.* do not disclose the preparation of full-length cDNAs, but instead disclose the preparation of long cDNAs. However, it is common knowledge for the skilled artisan that these are two difference concepts with different features and characteristics. A cDNA can be very, very long but still not full-length. For example a long cDNA (not

full-length) cannot be recovered according to the CAP trapper method (as disclosed by Carninci *et al.*, 1996, Genomics, 37:327-336) because they do not have the 5'end of cDNA. Other methods using a 3' primer method for recovering cDNA do not assure the recover of full-lengths. In fact, a complete cDNA library, as disclosed in Sambrook *et al.*, does not even suggest that full-length cDNAs are specifically prepared.

The Office Action asserts that it would have been obvious to one of ordinary skill in the art to apply the teaching of Sambrook *et al.* to Wagner *et al.* and prepare a full-length molecule and fix it on a chip. Applicants submit that this is not the case. Even now, full-length cDNAs were difficult to obtain. In support, Applicants again refer the Examiner to Momhaers, which support the assertion that full-length cDNAs are very difficult to obtain.

Thus, Applicant submits that without at least a suggestion of the use of full-length sequences by either of the cited references, the skilled artisan has no motivation or expectation of success at practicing the claimed invention. Further, the cited references doe not recite each element of the claimed invention.

Finally, the Office Action states that Applicant has not provided evidence that Sambrook *et al.* do not teach preparation of full-length cDNA. The legal concept of prima facie obviousness is a procedural tool of examination which applies broadly to all arts. It allocates who has the burden of going forward with production of evidence in each step of the examination process. The examiner bears the initial burden of factually supporting any prima facie conclusion of obviousness. If the examiner does not produce a prima facie case, the applicant is under no obligation to submit evidence of nonobviousness. *See In re Rinehart*, 531 F.2d 1048, 189 USPQ 143 (CCPA 1976), *In re Linter*, 458 F.2d 1013, 173 USPQ 560 (CCPA 1972), *In re Saunders*, 444 F.2d 599, 170 USPQ 213 (CCPA 1971 and M.P.E.P. § 2142. Applicant submits that the Examiner is improperly attempting to place the burden onto the Applicant. Applicant respectfully submits that the burden is not on the Applicant to provide the evidence. Rather, the burden is on the Examiner to show

where in the cited references there appears an indication of the preparation full-length cDNAs. The Examiner has not met this burden.

Accordingly, for the foregoing reasons, Applicant maintains that the presently claimed invention is neither anticipated by, nor obvious over, Wagner *et al.* Withdrawal of this rejection is thus respectfully requested.

Claim Rejections - 35 USC §103

The following rejections are set forth in the outstanding Office Action:

- Claim 5 stands rejected under 35 U.S.C. § 103(a) as purportedly unpatentable over the Wagner *et al.* (WO 93/02216) in view of Zoltukhin *et al.* (U.S. Patent No. 5,874,304).
- Claims 6-8 stand rejected under 35 U.S.C. § 103(a) as purportedly unpatentable over Wagner *et al.* (WO 93/02216) in view of Gifford (U.S. Patent No. 5,750,335).
- Claims 9-18, 22 & 33 stand rejected under 35 U.S.C. § 103(a) as purportedly unpatentable over Wagner *et al.* (WO 93/02216) in view of Chirildian *et al.* (U.S. Patent No. 5,763,178) and Goldrick (U.S. Patent No. 5,891,629).
- Claims 23-25 & 27 stand rejected under 35 U.S.C. § 103(a) as purportedly unpatentable over Wagner *et al.* (WO 93/02216) in view of Zoltukhin *et al.* (U.S. Patent No. 5,874,304) and Fleck *et al.* (Nucleic Acids Research, 1994, 22(24): 5289-5295).

Wagner *et al.* disclose the use of more nucleotide sequences as hybridization partners (see page 15, line 35) in the method known as "tiling". In contrast, the method of the present invention uses full-length cDNAs. The present invention requires only one full-length cDNA in order to be able to detect any mutation in the gene of interest. The method disclosed by Wagner *et al.* requires several oligonucleotides, and if the oligonucleotides do not cover the entire sequence of the gene, it is possible that mutations may be missed.

Applicant submits that the skilled artisan would not think that the disclosure of Wagner *et al.* includes full-length cDNAs. Wagner *et al.* only disclose short partner sequences, and never disclose or suggest full-length sequences. Specifically, Wagner *et al.* disclose that the hybridization partner is about 20 to 100 nucleotides in length, and preferably, 20 to 40 nucleotides in length). Wagner *et al.* provides no suggestion or motivation for the skilled artisan to extrapolate a full-length cDNA for a hybridization partner, because the disclosure of Wagner *et al.* not only fails to disclose or suggest full-length sequences, but also teaches that short sequences of 20 to 40 nucleotides are preferable.

As already discussed above, the preparation of full-length cDNA requires particular skills and methods. At the time the invention was filed, and even today, it is very difficult to obtain full-length cDNAs. Thus, without any clear motivation to prepare a full-length cDNA for hybridization, the skilled artisan, knowing the difficulty associated with preparing full-length cDNAs, would not attempt to prepare full-length cDNAs. Rather, they would prepare the small sequence fragments which Wagner *et al.* teach are preferable. Wagner *et al.* disclose a hybridization method which requires the use of fragments. Further, Wagner *et al.* discloses to the skilled artisan that the method will work more efficiently the more fragments are used. Thus, the skilled artisan is motivated to use more fragments, rather than one full-length fragment. Thus, the skilled artisan would not have any motivation nor any expectation of success, to modify the disclosure of Wagner *et al.* to arrive at the presently claimed invention.

Finally, Applicant notes that Wagner *et al.* is non-enabling for the preparation of full-length sequences. A prior art reference must be enabling, thus placing the allegedly disclosed matter in the possession of the public. *Akzo N.V. v. International Trade Commission*, 1 USPQ 1241, 1245 (Fed. Cir. 1986). Because Wagner *et al.* specifically cite Sambrook *et al.* as the preferred protocol for preparing hybridization partners, and Sambrook *et al.* do not disclose or even suggest making a full-length sequence, the preparation of a full-length sequence is not enabled by Wagner *et al.*

The secondary references, Zoltukhin *et al.*, Gifford, Chirildian *et al.*, Goldrick and Fleck *et al.* fail to remedy the deficiencies of the primary reference. Accordingly, the presently claimed invention is not *prima facie* obvious over Wagner *et al.* The Applicant requests that this rejection be withdrawn.

The following rejections are also set forth:

- Claims 4 and 5 stand rejected under 35 U.S.C. § 103(a) as purportedly unpatentable over Chee *et al.* (U.S. Patent No. 5,861,242) in view of Zoltukhin *et al.* (U.S. Patent No. 5,874,304).
- Claims 9-18 stand rejected under 35 U.S.C. § 103(a) as purportedly unpatentable over Chee *et al.* (U.S. Patent No. 5,861,242) in view of Chirkjian *et al.* (U.S. Patent No. 5,763,178) and Goldrick (U.S. Patent No. 5,891,629).
- Claim 23 stands rejected under 35 U.S.C. § 103(a) as purportedly unpatentable over Chee *et al.* (U.S. Patent No. 5,861,242) in view of Zoltukhin *et al.* (U.S. Patent No. 5,874,304).
- Claim 24 stands rejected under 35 U.S.C. § 103(a) as purportedly unpatentable over Chee *et al.* (U.S. Patent No. 5,861,242) in view of Zoltukhin *et al.* (U.S. Patent No. 5,874,304) as applied to Claim 23 above and further in view of Fleck *et al.* (Nucleic Acids Research, 1994, 22(24): 5289-5295).
- Claim 25 stands rejected under 35 U.S.C. § 103(a) as purportedly unpatentable over Chee *et al.* (U.S. Patent No. 5,861,242) and Fleck *et al.* (Nucleic Acids Research, 1994, 22(24): 5289-5295).
- Claim 27 stands rejected under 35 U.S.C. § 103(a) as purportedly unpatentable over Fleck *et al.* (Nucleic Acids Research, 1994, 22(24): 5289-5295) and Chee *et al.* (U.S. Patent No. 5,861,242) in view of Zoltukhin *et al.* (U.S. Patent No. 5,874,304).

Applicant submits that Chee *et al.* is not properly cited. As discussed above, the methods of the present invention comprise the essential step of hybridization of the target nucleic acid with the full-length cDNA fixed on the support. In contrast, Chee *et al.* disclose methods wherein the target nucleic acid does not hybridize with the reference full-length, but with short oligonucleotide probes. In fact the reference sequence and the target sequences are sense sequences of each other and thus, are not capable of hybridizing. Therefore, Chee *et al.* does not disclose the steps of the method of the invention.

Applicant respectfully requests that the rejections be withdrawn.

CONCLUSION

From the foregoing, further and favorable reconsideration in the form of a Notice of Allowance is believed to be next in order and such action is earnestly solicited.

In the event that there are any questions concerning this amendment, or the application in general, the Examiner is respectfully urged to telephone the undersigned so that prosecution of this application may be expedited.

Respectfully submitted,

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Attachment to Reply and Amendment

Marked-Up Claims 1 and 9

1. (Four times Amended) A method for detecting nucleic acid fragment and/or PNA having a mutation, comprising the steps of:

(A) hybridizing at least one full length cDNA [fragment among one or more fragments] fixed on a substrate, [which fragments are] selected from the group consisting of one or more nucleic acid fragments and one or more PNA fragments and have all of a cDNA [sequence of full-length gene], with at least one fragment of which mutation is to be assayed, wherein said fragment is selected from the group consisting of one or more nucleic acid fragments and one or more PNA fragments, thereby hybridizing fragments having a mutation;

(B) binding a labeled protein [having a label, said protein] specifically [binding] to a mismatched base pair occurring between the hybridized fragments having a mutation; and

(C) identifying a fragment bound by the labeled protein by detecting the label, thereby detecting a nucleic acid and/or PNA fragments having a mutation.

6. (Three Times Amended) The method of claim 1, wherein the method further comprises introducing a label into a nucleic acid and/or PNA fragment to be assayed for mutations, and detecting the label of the nucleic acid and/or PNA fragment to be assayed for mutations, are carried out in order to identify and quantify the fragment having a mismatched base pair.

9. (Three Times Amended) A method for detecting a nucleic acid fragment and/or PNA fragment having a mutation, comprising the steps of:

(A) hybridizing at least one full-length cDNA [fragment among one or more fragments] fixed on a substrate, [which fragments are] selected from the group consisting of one or more nucleic acid fragments and one or more PNA fragments

and have all of a sequence of a cDNA [full-length gene], with at least one fragment of which mutation is to be assayed, wherein said fragment is selected from the group consisting of one or more nucleic acid fragments and one or more PNA fragments, thereby hybridizing fragments having a mutation;

(D) treating a mismatched base pair occurring between the hybridized fragments with a protein specifically recognizing and cleaving the mismatched base pair to cut the hybridized fragments at the mismatched base pair, or to remove at least a part of one strand of the fragments hybridized from the mismatched base pair;

(E) labeling a fragment remained on the substrate after the cleavage or removal; and

(F) identifying the labeled fragment by detecting the label, thereby detecting a nucleic acid and/or PNA fragment having a mutation.